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PHAEDON KAKLAMANIS[1], ANDRZEJ GRZYBOWSKI[2, 3],
GERASIMOS D. PALIMERIS[4], VIRGINIA KAKLAMANI[5], CHRISTOS C. ZOUBOULIS[6]

# The First Published Case of Adamantiades-Behçet's Disease in the Modern Times — Revisited

## Pierwszy opublikowany przypadek choroby Adamantiadesa-Behçeta w czasach nowożytnych — ponowna analiza

[1]Medical Center, Athens, Greece; [2]Department of Ophthalmology, Poznań City Hospital, Poznań, Poland; [3]Department of Ophthalmology, University of Warmia and Mazury, Olsztyn, Poland; [4]Ophthalmologic Clinic, Athens, Greece; [5]Cancer Genetics Program, Division of Hematology/Oncology, Department of Medicine and Robert H. Lurie Comprehensive Cancer Center, Feinberg School of Medicine, Northwestern University, Chicago, IL, USA; [6]Departments of Dermatology, Venereology, Allergology and Immunology, Dessau Medical Center, Dessau, Germany

**Summary**
The first case of the so-called Adamantiades-Behçet's disease was presented by Benediktos Adamantiades in the annual meeting of the Medical Society of Athens on 15th November 1930 under the title "A case of recurrent iritis with hypopyon". It was published in the proceedings of Athens Medical Society in 1930. This paper, including an English translation of this presentation, provides proof that Adamantiades was aware that he was describing a new clinical entity.

**Keywords:** Benediktos Adamantiades, Adamantiades-Behçet's disease, Behçet's disease, history

**Streszczenie**
Pierwszy przypadek choroby Adamantiadesa-Behçeta został przedstawiony przez Benediktosa Adamantiadesa na dorocznej konferencji Ateńskiego Towarzystwa Medycznego 15 listopada 1930 roku pod tytułem „Przypadek nawracającego zapalenia tęczówki z ropostekiem". Wystąpienie zostało opublikowane w sprawozdaniach z Ateńskiego Towarzystwa Medycznego z 1930 roku. Obecna praca dostarcza, wraz z angielskim tłumaczeniem oryginalnego tekstu, dowodu, że Adamantiades był świadomy odkrycia nowej jednostki chorobowej.

**Słowa kluczowe:** Benediktos Adamantiades, choroba Adamantiadesa-Behçeta, choroba Behçeta, historia

### Introduction

For many years it was believed that the first description of so called Behçet disease, defined as the classical clinical triad of recurrent oral aphthous ulcers, genital ulcers and iritis/uveitis [1], was due to Hulûsi Behçet (1889–1948), a well-known Turkish dermatologist. However, the first description of a case of the disease in the modern times is attributed to Benediktos Adamantiades (1875–1962) [2, 3], a Greek ophthalmologist from Prousa, Asia Minor (now known as Bursa, Turkey).

Adamantiades graduated at the Medical School of the University of Athens in 1896 with distinction. The lectures of the renowned professor of ophthalmology, A. Anagnostakis, aroused his special interest in the field. Due to financial problems he had to practice as a general practitioner in Prousa for the 10 subsequent years. Then he went to Paris where he was trained in ophthalmology in the years 1911–1914. After the outbreak of the First World War he returned to Prousa, was mobilized to serve as an officer-physician in the

Turkish army and because of a severe gastrointestinal disease he was dismissed one year later. At the end of the war he was elected president of the Greek community of the Prousa city, and in the years 1920–22 he was involved in the re-establishment of Greek health administration and Greek language schools for minors and adults. In 1922 he accompanied millions of Asia Minor inhabitants of Greek origin as a refugee to Greece. He started his work as an ophthalmologist in Athens, where he became in 1924 Director of the Ophthalmology Department of the Refugee Hospital of Athens[1]. Adamantiades was a founding member of the Greek Ophthalmologic Society in 1931. He married at a late age and died in 1962. His adoptive daughter, Urania Rangavi, was the first female ophthalmologist in Greece [2].

At present, the majority of the specialists, who study this disease are aware of Adamantiades' publication in the Annales d'Oculistique in 1931 [4], which has been included by Hulûsi Behçet in the references of his first publication in 1937. However, some authors have disputed the recognition of the disease as a new entity by Adamantiades despite his description of the complete recurrent array of signs (iritis, skin lesions, arthritis, aphthae, scrotal ulcers) in 1931 [5]. Therefore, we would like to present a much less known earlier publication in the Greek language, which reports on the initial presentation of this first case report by Adamantiades at the annual meeting of the Medical Society of Athens on November 15, 1930 [6, 7]. This case report and the subsequent discussion at the Medical Society of Athens [6], which has been translated here into English, provides proof that Adamantiades was aware that he was describing a new clinical entity, which he named "Relapsing iritis with hypopyon". This is additional argument for the present use of a more appropriate name of the disease — Adamantiades-Behçet's disease — as it was previously proposed [2, 3, 5, 7].

**Report**

**A case of recurrent iritis with hypopyon**

by BENEDIKTOS ADAMANTIADES

Cases of recurrent iritis with hypopyon are not so common; their etiology is not clearly defined. This is why I wanted to present a case of this peculiar disease, which I have continuously followed over 3 years.

Gr. X., age 20 years old first came to the Refugees Hospital in Athens in June 1928. His father died as a prisoner in Smyrna. His mother died due to chronic bronchitis and spitting blood. Two of his sisters died at a young age. He denied a history of gonorrhea or syphilis. At the age of 16 he suffered from malaria.

In 1925–26 ulcerations appeared on his left leg accompanied by edema. Some doctors considered that these findings were due to phlebitis, others, considered it a manifestation of syphilis in spite of the negative Wassermann reaction, and others as pyodermatitis and treated him with autovaccination (rem. auth. reinjection of thermally treated serum of the patient with supposed killed bacteria).

In 1927, his eyes became affected for the first time. In the Outpatient Clinic in Kessariani (rem. auth. suburb of Athens) we diagnosed him with iritis with hypopyon. The Wessermann reaction was weekly positive. It was the only positive reaction he had. Since then these episodes of iritis with hypopyon continued alternating between the left and right eye.

Sometimes increased secretions from the nasopharynx preceded the attack. Simultaneously scrotal ulcers developed, which were frequently recurrent. He did not have erythema nodosum and his teeth were normal. A few months ago he lost vision in the left eye and two days ago the right eye was again affected. We noted that antisyphilitic therapy did not change the clinical course.

Present condition: Right eye: Hyperemia of conjunctiva, intense perilimbal injection; very few precipitates on the cornea; thick iris with fine posterior synechia, hypopyon 1 mm height; the fundus cannot be seen; intense pain around the orbit, visual acuity (V.A.): light perception. Left eye: phthisis bulbi. No anterior chamber abnormalities. Anomalous pupil margin. The fundus has a green reflection. Severe pain around the orbit. Ciliary area very painful on contact.

On auscultation the lungs were clear. Chest examination with X-rays showed enlargement of the lung hilar nodes. The Wassermann reaction was again negative. Antisyphilitic treatment was continued without any success and this was combined with local therapy.

In 5–6 days the posterior synechiae of the right eye started to disappear, the pupil dilated and the hypopyon was absorbed. Although the vitreous body was cloudy, the fundus appeared better. The optic disc was pale and the vessels attenuated. At the end of the second month the patient had V.A. 0.05. Meanwhile, we have enucleated the left eye which had phthisis bulbi and was very painful. On the 24$^{th}$ of August 1928 hypopyon appeared again with very mild iritis but was absorbed quickly and the fundus was able to be examined. The patient has V.A. 0.1.

[1] Now known as Hippokration Hospital.

For the past two months ago we combined antisyphilitic treatment[2] with tuberculin injections.

On December 29, 1928 we tried to treat him with proteinotherapy, however, severe reactions developed and we discontinued it. Hypopyon appears again February 11, 1929. It was subsequently absorbed and appeared again on February 19 of the same year. With each relapse, his amblyopia increased. During this time he had recurrent scrotal ulcers which disappeared after a few days and recurred soon thereafter. On March 5 he was discharged from the Hospital with fine posterior synechiae and hemidilated pupil, cloudy vitreous, intraocular pressure 11/7.5 and visual acuity at the level of "counting fingers from one meter". The patient after his discharge from the Hospital continued his antisyphilitic therapy, but hypopyon appeared again during the treatment and on June 27, 1929 he was again admitted to the Hospital.

Chest examination with X-rays showed similar findings as previously. On examination, chronic pharyngitis and tonsillitis were found. On examination of the tonsilar smears staphylococcus was cultured. His left knee was swollen. Five to six scars of 8–10 mm diameter were found on the leg. On the scrotum three round ulcerations with clear bottom and scars from previous ulcerations which were characterized as syphilitic or herpes exanthema by other doctors, were found. Lymph nodes of the groins, axilla and left cervical area were enlarged. Ulcers in the mouth were also found. He was again found to have iritis with hypopyon. The red reflex was absent. The patient had vague projection of light. We continued treatment with B1[3]. The hypopyon was absorbed but appeared again on August 8, 1929. Subsequently his eye remained without any signs of inflammation and on December 4, 1929 we performed an iridectomy. Five days after iridectomy, hypopyon appeared and was absorbed within a few days and reappeared on January 16, 1930 and later on February 20, 1930.

We tried to induce technical pus with injections of electrargol[4] and sodium salicylate but were unsuccessful. With puncture of the anterior chamber of the eye, pus came out which was sterile and the inoculation in rabbit's eye induced inflammation with negative culture. He was admitted a second time to the Hospital and was found to have hydrarthrosis in one and subsequently the other knee. The hydrarthrosis rapidly subsided and within a few days to weeks recurred again without any reactive component or X-ray findings. In 3–4 months, the repeated punctate of the swollen knee produced a clear fluid which turned into a cloudy fluid but cultures were negative. During the same time recurrent mouth aphthous ulcers and a tonsilar abscess were seen. Hypopyon appeared again on March 19, April 2, April 15 and May 29. In June, culture taken from the scrotal ulcers were negative for treponema and positive for staphylococcus.

Cerebrospinal fluid showed 0.25 gr/l protein, 0.50 gr/l sugar and a negative Wassermann reaction. Lymphocytes were rare. On the 21st and 28th of July as well as 5th and 12th of October hypopyon appeared with very mild iritis. On October 3, staphylococcus was cultured from the blood. The autovaccination[5] induced fever. His present condition (1st of November) is as follows: Cornea with diffuse fine precipitates, some of which form plaques in the anterior layers of the stroma. The iris is atrophic, almost flat without cysts and crypts. The free margin of iris has a width of 1½–2 mm consisting of pigmented epithelium. On the lens there are a few pigment deposits. The fundus cannot be examined easily but a white optic disc is seen. He has a vague perception of light.

We have in front of us a clinical picture, which Gilbert (K. Handbuch der Ophthalmologie t.v.) named ophthalmia lenta. The main characteristic of the disease is the development of hypopyon without reactive phenomena in different times, characterized by a rapid absorption. Each attack leaves permanent damage which leads to blindness. In our case blindness, according to Meller, was the result of the atrophy of the optic nerve due to the dead remnants of the vitreous body which passed through the sheaths of the optic nerve. Sometimes hyperaemia of the ciliary body, which usually appears a few hours before the formation of hypopyon, retreats without the formation of hypopyon.

The variety of the treatments used, and their lack of efficacy, proves the uncertainly of the etiological factor of the disease. What is the etiology of this iritis in our case? This is the problem we are facing with. We could rely on two observations in order to find the etiological factor of each or every iritis, 1) on the mode of appearance with which this started, 2) on the results, which the general examination or the coexistent manifestations will provide us. The mode of appearance rarely helps the diagnosis. Syphilitic or tuberculous iritis could manifest either with diffuse nodules or as serous with

[2] Antisyphilitic treatment at that time included intravenous injections of arsen [m-diamino-p-dioxy-arsenobenzol dichlorhydrate 20% solution] or tryparsamide, a synthetic arsenic solution as well as of bismuth [potassium and sodium tartro-bismuthate oily solution].

[3] Vitamin B1.

[4] Electrargol was a liquid preparation of colloidal silver, obtained electrically. It contained ultra-microscopic particles of metallic $Ag^{3+}$ in suspension, forming a colloidal solution.

[5] Reinjection of thermally treated serum of the patient with killed staphylococci.

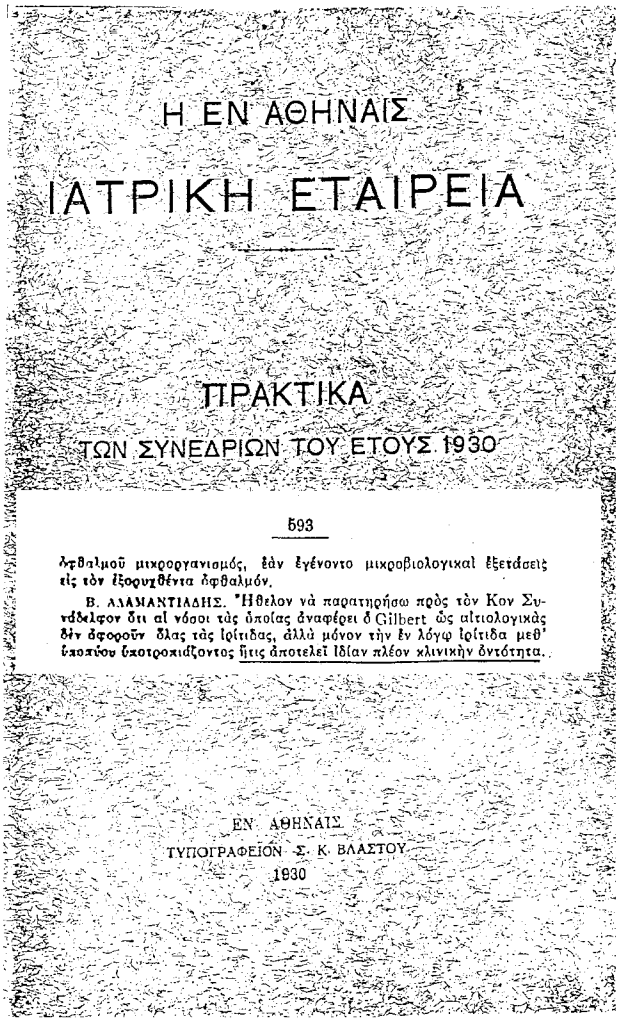
many keratic precipitates or as fibrinous with synechiae and hypopyon. Viennemen (Encycl. fr. t.v.p.6) has said that the body reacts in the same way against different stimuli. In the present case the review of the course of the disease and the mode of appearance do not help elucidate the etiology.

Reis in 1906 first described the metastatic iritis (Kl. Mon. f.A) following erythema nodosum. Kopper in 1917 presented a similar case (Gr. Arch). Gilbert in 1920 (Arch f.A.) considers that the disease is a particular manifestation of erythema nodosum. Stahli in 1922 (Kl. M.F.A. 1922) believed that the cause of the disease is tuberculosis. Weve in 1923 considered staphylococcal infection as the etiologic factor. Urbanerva described (Zeits.f.A. 1929) two cases and insisted that the etiological factor was tuberculosis. Gilbert (1930 K. Hand. Der A.) describing the iritis expressed the opinion that iritis is due to acute or chronic infections or purulent infections in which he included erythema nodosum, pyodermatitis, furuncles, arthritis, abscess etc. He also insists that in one case in the blood and in the purulent infected sites staphylococcus was isolated. We can conclude that there is uncertainty between different writers as far as the etiology of this disease.

Let us review the general situation of our patient which could give us a basis for finding the etiology of the disease. After studying the clinical and laboratory findings in the patient could lead us in three directions: 1) tuberculosis 2) syphilitic infection or 3) infection particularly staphylococcal from another site. The patient had hereditary predisposition to tuberculosis and a chest X-ray with enlarged hilar lymph nodes. It is known that tuberculosis can play a considerable role in eye diseases and particularly in uveitis. Michel, Meller, Gilbert consider tuberculosis responsible for 50% of iritis. Iritis could be the result not only of severe cases but also of less severe cases of tuberculosis, where after intense investigation tuberculosis was discovered. However, we do not think that in our case tuberculosis was the etiological factor of the iritis but cannot exclude this possibility. As far as the possibility that the etiology of these manifestations is syphilis, our dermatologists believe that this is the case and the resistance to the three specific medications points toward resistant disease. We concede that there is a possibility that some of these manifestations may be syphilitic, however we doubt that the iritis can be attributed to syphilis and do not believe that such a generalized presentation can be a manifestation of syphilis. We conclude that the failure of antisyphilitic treatment and the repeated negative Wassermann reaction leave no doubt in our minds that syphilis is not the etiology of the disease.

FIG. 1. Benedictos Adamantiades (1875–1962), former director of the Ophthalmology Department of the Hippocration Hospital. Source: Zouboulis C.C., Keitel W., *A Historical Review of Early Descriptions of Adamantiades-Behçet's Disease* [w:] *Journal of Investigative Dermatology* 2002, 119, 201–205

Let us review the third possibility. Clinically we have the impression that the scrotal skin manifestations, the arthritis of the knees and those of the iris have the same mode of appearance; after they develop, they persist for a few days and then subside, leaving some traces depending on the site. They then recur without any obvious cause and without any treatment that can stop their evolution or their reappearance. If we combine those findings with laboratory findings e.g. the isolation of staphylococcus from the scrotal ulcers, from pharynx and blood we can accept the theory of a local infection as the etiological factor. Local infection plays a very important role in medicine in English speaking countries. Several, e.g. local or generalized infections are accepted to be initiated by the presence of bacteria in a hidden site of the body. These infections can cause more serious manifestations, e.g. infection of the tonsils, teeth or prostate. It is possible that in our case the repeated hypopyon was due to the bacteria in the circulation (transient but repeated bacteriemia) migrating to the iris. The finding of staphy-


Η ΕΝ ΑΘΗΝΑΙΣ

ΙΑΤΡΙΚΗ ΕΤΑΙΡΕΙΑ

ΠΡΑΚΤΙΚΑ

ΤΩΝ ΣΥΝΕΔΡΙΩΝ ΤΟΥ ΕΤΟΥΣ 1930

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ὀφθαλμοῦ μικροργανισμός, ἐὰν ἐγένοντο μικροβιολογικαὶ ἐξετάσεις εἰς τὸν ἐξορυχθέντα ὀφθαλμόν.

Β. ΑΔΑΜΑΝΤΙΑΔΗΣ. Ἤθελον νὰ παρατηρήσω πρὸς τὸν Κον Συνάδελφον ὅτι αἱ νόσοι τὰς ὁποίας ἀναφέρει ὁ Gilbert ὡς αἰτιολογικὰς δὲν ἀφοροῦν ὅλας τὰς ἰρίτιδας, ἀλλὰ μόνον τὴν ἐν λόγῳ ἰρίτιδα μεθ' ὑποπύου ὑποτροπιάζοντος ἥτις ἀποτελεῖ ἰδίαν πλέον κλινικὴν ὀντότητα.

ΕΝ ΑΘΗΝΑΙΣ
ΤΥΠΟΓΡΑΦΕΙΟΝ Σ. Κ. ΒΑΑΣΤΟΥ
1930

FIG. 2. Cover page of 1930's "Archives of the Athens Medical Society". Source: Zouboulis C.C., Kaklamanis P., *Early descriptions of Adamantiades-Behçet's disease* [w:] *Ann Rheum Dis* 2003, 67, 691–692

lococcus in the blood, tonsils and scrotal ulcers lead us to consider the possibility that the periodic bacteriemia would cause the periodic localization to the iris.

## Discussion

V. VASSILOPOULOS: The case reported by my colleague is a case of metastatic ophthalmia and the cause is far away from the diseased eye. In the bibliography we can find several reports of similar cases. All the infectious diseases, not just the one discussed by my colleague, which manifested with typical signs such as scrotal ulcers etc., can be the causative mechanism. We had a case of iritis with hypopyon in a person who also suffered from infection of a lymph node of the right groin following a soft ulcer of the penis. When we subsequently opened the lymph node of the groin, pus came out and the swelling subsided, but in a few days enlargement of a lymph node of the left groin appeared and when we opened it, pus came out again and then the swollen lymph node subsided. In relation to the metastatic ophthalmia, the reason why the opinions of ophthalmologists differ, is the following: what is the causative agent of metastatic ophthalmia, is it a microorganism or toxins. In the bibliography, Tornatola first in 1890 at the congress of Italian Ophthalmologists presenting the work on metastatic diseases of the eye concluded, based on experimental and clinical work by several investigators, that there are two ways for this to happen: a) via the circulation there is transport of pathogenic microorganisms to the eye or b) via transportation of toxins to the eye. In the first case transportation of infectious agents induce a purulent collection, as shown in several reports, while in the second case the transport takes place only in pathological conditions without pus formation, such as haemorrhages and venous thrombosis. In 1910 we performed experiments on metastatic diseases to the cornea and iris with streptococcus, staphylococcus, pneumonococcus and E.coli and we published our observations. Our results were in agreement with those of others and concluded that the metastatic diseases of the eye are due to the microorganisms. We were never able to confirm the presence of toxins. We were then able to follow the progression of the eye diseases and found it to be dependent on the distant infection. I would therefore add that in the case that my colleague presented the microorganism cultured is responsible for the recurrences in the eye since it was found when cultures were performed in the enucleated eye.

B. ADAMANTIADES: I wanted to respond to my respected colleague that the disease entity, which Gilbert mentioned as "etiologic", may not be associated with all iritis types and that this case of iritis with recurrent hypopyon, now constitutes itself a clinical entity.

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